Clinical Perspectives on Diabetes

Satellite Conference
Thursday, March 10, 2005
2:00-4:00 p.m. (Central Time)

Produced by the Alabama Department of Public Health
Alabama Public Health Training Network

Faculty

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Auburn, Alabama

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Director of Diabetes Complications and Prevention Treatment Clinics
Montgomery, Alabama

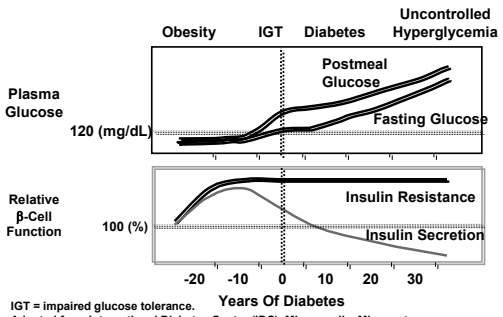
Objectives

1. To discuss the latest recommendations in diabetes treatment.
2. To provide three recent case studies along with treatment modalities for diabetes and cardiovascular disease.
3. To discuss at least five current pharmacology options for diabetes management.

Diabetes Treatment

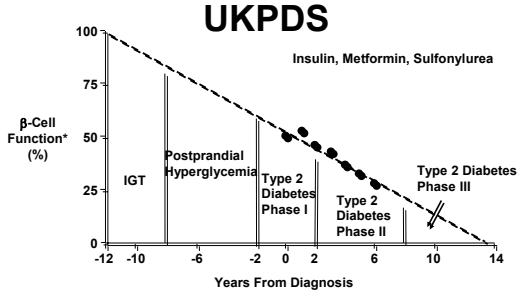
Michael Hennigan, MD, FACP

Natural History Of Type 2 Diabetes



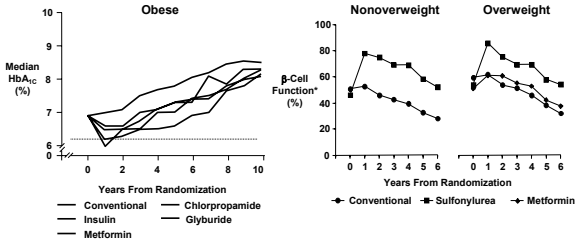
IGT = impaired glucose tolerance.
Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.

Decline In B-Cell Function In UKPDS



*HOMA = homeostasis model assessment; IGT = impaired glucose tolerance. Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS. Lebovitz. *Diabetes Rev*. 1999;7:139-153. UKPDS Group. UKPDS 16. *Diabetes*. 1995;44:1249-1258.

B-Cell Failure Not Prevented When Therapy Delayed

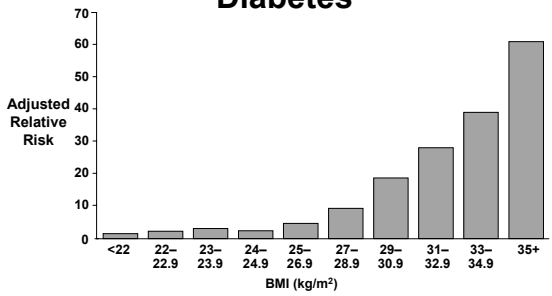


Adapted from UKPDS Group. *Lancet.* 1998;352:854-865.

UKPDS Group. *Diabetes.* 1995;44:1249-1258.

*As measured by homeostasis model assessment.

Body Mass Index (BMI) and Relative Risk Of Type 2 Diabetes



In women 35-55 years of age in 1976; data adjusted for age.
Adapted from Colditz et al. *Am J Epidemiol.* 1990;132:501-513.

Changes in Diabetes Definition

Year	Normal
• Prior to 1998	FBS < 140
• 1998	FBS < 125
• 2000	FBS < 110
• 2003	FBS < 100

Therapy Options

- Before 1995 Increase insulin supply
- 1995 Metformin (Glucophage)
- 1998 Troglitizone (Resulin)
- 1999 Rosiglitazone (Avandia) and Pioglitazone (Actos)

Patient #1

- 27 WM Completed Masters at Auburn 2004
- Dx Type II Diabetes 2001 at MD office
- Placed on Diet/Exercise and Metformin + TZD as glucose elevated further
- Lost 30# on diet and exercise, states little effort required, yet BS > 300
- Moved to Decatur, seen October 2004

Patient #1

- Initial Lab October 2004
  - HbA1c 12.5%
  - Urine Protein +2, Glucose +4, Ketone +1
  - C-Peptide < 0.5, Insulin < 2
  - GAD, Islet Cell Antibody Positive
  - Cr 0.8, BUN 27

  –NEXT MOVE ???

Patient #1

- Began Insulin Glargine (Lantus) QD + Novolog with each meal (correction factor and 1unit:10 gm carbohydrate
- Stopped Metformin and TZD
- Added ACE (Altace) due to proteinuria

Patient #1

- 3 Month Follow-Up
- HbA1c 7.1%
- BP 125/68
- Wt 183 (up 8#), BMI 24
- Urine Protein Dipstick Negative

Patient #2

- 54 WF Dx Type I DM age 18 (1969)
- Placed on Split/Mixed regimen at diagnosis
- Wt ~ 175#, BMI 29 - 1969
- Gained to 235# over next 10 years
- Insulin increased to > 200 units per day yet HbA1c 11.2%

Patient #2

- Complications
  - MI X 2
  - CABG 2003
  - Peripheral Vascular Disease – Amputation all toes left foot 2001
  - Nephropathy –
    - –24 Hr Urine Protein 3720mg
    - –(N < 150mg/24 hrs)
    - –Creatinine Clearance 24 cc/min
    - –(N > 80 cc/min)
    - –Creatinine 1.3, Bun 69
  - Retinopathy
    - –Laser Coagulation x 3 with loss of ~ 40% of vision

Patient #2

- C-Peptide 4.1 (N 0.8 – 3.1)
- Chol - 197; HDL - 47; Trig - 349; LDL - 81
- BP - 136/80
- LVH on ECG, LV prominence on CXR
- Wt - 215; Ht - 64”; BMI - 36.3

Patient #2

- Diagnosis: Type II Diabetes with marked insulin resistance, diabetic nephropathy, retinopathy, neuropathy, vasculopathy.
- Hypertensive Heart Disease with LVH
- Hyperlipidemia
- Peripheral Vascular and Cardiovascular Dz.

Patient #2

- Treatment
  - Metformin 500mg QD
  - Actos 15mg x 2 weeks, then 30mg qd
  - Instructed to decrease insulin as BS fell to under 120
  - Low carbohydrate (20 gm per meal) recommended
  - Exercise daily as tolerated (Medicaid would not cover water aerobics at local Physical Therapy)
  - Lisinopril (Prinivil), Simvastatin (Zocor), Coreg

Patient #2

- Initial Follow-up 1/05/05
  - BUN 57, Cr 1.3
  - Creat. Clearance 46 cc/min
  - 24 Hr Urine Protein 4015 mg
  - HbA1c 7.5%
  - C-Peptide 3.4 (Done to confirm for patient)
  - Now on 40 units Lantus QD (Down from > 200u)

Patient #3

- 61 BM presented Feb 2000 with 20 year hx. AODM
- HbA1c 9.8% on Amaryl 4mg bid
- Added Metformin and Actos
- 06/01/00 HbA1c 6.9% on triple therapy
- 10/23/00 HbA1c 7.4%
- 02/08/01 HbA1c 11.1%, C-peptide 1.1, Insulin 4
- Insulin added, and Amaryl stopped

Diabetes Treatment Summary

- Evaluate for insulin deficiency and insulin resistance and Rx each on own merit
- Address lipids, BP, aspirin as coronary artery disease equivalent
- Follow and Rx proteinuria on its own
- Average HTN/DM patient requires 3.9 meds to control to guidelines
- Diabetes education, eye and foot exam QY

Diabetes Treatment Summary

- If aggressive comprehensive treatment and educated compliance: complications can be delayed or prevented
- "Tell me 'O Spirit, Is this the way I must be, or the why it may be, and if I change may it change also."
  - Ebenezer Scrooge to the Ghost of Christmas Future in Dickens "A Christmas Carol"

Therapeutic Pearls for Diabetes

Pamela L. Stamm, PharmD

Objectives

- Identify antidiabetic drugs that reduce CV events
- Create regimens that minimize weight gain
- Understand the evidence behind dietary supplements used for self-management (cinnamon, ginseng)
- Recognize upcoming therapies for diabetes

Cardiac Risk and Diabetes

- 65% of all diabetic deaths due to CVD
- Rates of CVD death are declining
- Primary prevention: risk of CHD event equal to non-diabetics with known CHD
- Secondary prevention: risk greater than non-diabetics with known CHD

Geiss LS *Diabetes in America*. 1995:233-257. Haffner SM et al. *N Engl J Med* 1998;339:229-34. Wingard DL *Diabetes in America*. 1995:

Cardiac Risk and Diabetes

- UKPDS
  - Tight glycemic control did not reduce CV events
  - Neither insulin or oral sulfonylurea use reduced CV events

UKPDS 33. Lancet 1998;352:854-865.
UKPDS 34 Lancet 1998;352:854-865.

Reducing Cardiac Events

Through tight control with metformin in overweight Type 2 diabetics

Endpoint	NNT
Any DM endpoint	10
All cause mortality	14
Nonfatal or fatal MI	16

UKPDS 33. Lancet 1998;352:854-865.
UKPDS 34 Lancet 1998;352:854-865.

Reducing Cardiac Events

STOP NIDDM

- Acarbose 100 mg TID (n=682) vs Placebo (n=686)
- Mean duration 3.3 years

	HR (95% CI)	P value	NNT
CV events	.51 (.49 .89)	.03	40
Clinical MI	.09 (.01 .72)	.02	6
Any CV event	.51 (.28 .95)	.03	37

Chiasson JL. J Am Med Assoc 2003; 29: 486-494.

Reducing All-Cause Mortality Post-MI

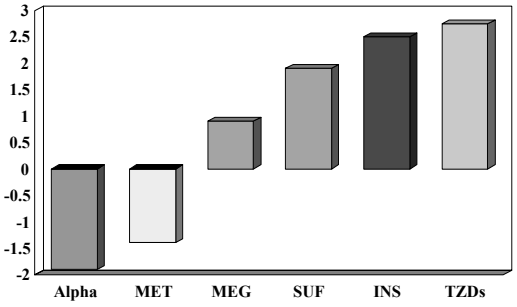
DIGAMI (n = 620)

- Used insulin infusions followed by tight control with SQ insulin injections for at least 3 months
- Followed for 27 months

	RRR	P	NNT
Mortality			
In hospital	18	NS	--
3 month	21	NS	--
1 year	29	0.273	14

Malmerg K. J Am Coll Cardiol

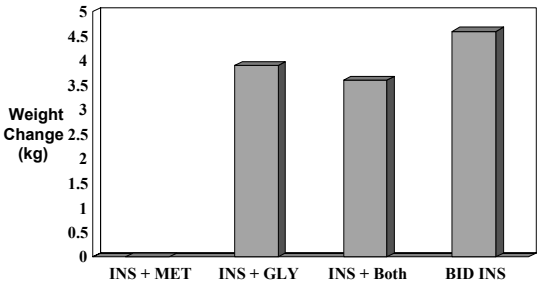
Weight Changes with Monotherapy



Weight Changes With Oral Combinations

- Acarbose reduces weight gain with SFU and MEG not TZDs
- Metformin reduces weight gain associated with SFU, TZD, INS
  - –The order of addition may matter

Weight Changes With Insulin And Oral Combinations



Yki-Jarvinen H. Ann Int Med 1999;130:389-396.

Minimizing Weight Gain

- Add metformin to regimen
- Add metformin to insulin regimen prior to addition of TZD and delay addition of TZD for 4 months

Metformin ADRs

- Diarrhea: most common dose related ADR
- Mechanism: ↓ bile acid re-absorption from gut
- Prevention: titrate MET dose beginning at 500 mg QD or BID with food
- Treatment: can add BAS (ie, questran lite, colesevelam)

Metformin – Lactic Acidosis

- Guilt by association
  - –Phenformin 40-64 : 100 000 pt years
  - –Metformin 2-9 : 100 000
- Problems with trials / case reports
  - –Most trials excluded persons at high risk
  - –Lactate levels did not parallel metformin concentrations
  - –Retrospective analyses limited by sample size
  - –Most cases had other risk factors present

Salpeter S. *Arch Int Med* 2003; 163: 2594–2602
Misbin RI. *Diabetes Care. 27(7):1791-3, 2004 Jul.*

Metformin – Lactic Acidosis

Contraindications

- **Cr > 1.4 females; 1.5 males**
- **CHF requiring therapy**
- **Chronic or acute metabolic acidosis**
- **Cardiovascular collapse**
- **Within 48 hours of contrast dye. Should withhold until receipt of normal Cr**

Metformin PI. Bristol Meyers Squibb. www.BMS.com March 2004

Dietary Supplements

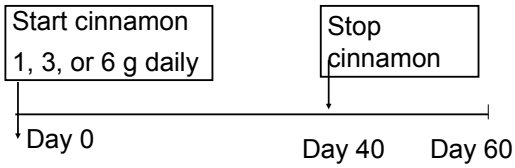
Cinnamon **Ginseng**

Cinnamon (*Cinnamomum cassia*)

- **Objective: Determine dose response on glucose and lipid parameters vs placebo**
- **Population:**
  - **Type 2 DM with FBG 140-400 mg/dL**
  - **Not on insulin or non-diabetic medications**
  - **Age 52**
  - **Duration of diabetes 6.73 y (P) and 7.1 y (C)**

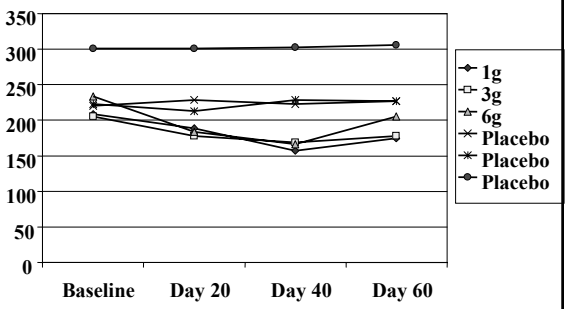
12121.hostinguk.com/ spicephotos.htm
Khan A. Diabetes Care 2003;26:3215-3218.

Cinnamon



Khan A. Diabetes Care 2003;26:3215-3218.

Cinnamon versus Placebo



Khan A. Diabetes Care 2003;26:3215-3218.

American Ginseng

(Panax quinquefolius)

Healthy adults

- **No dose response (1 - 9g ginseng)**
- **Must take at least 40 minutes and up to 2 hours before the meal**

Diabetics

- **No dose response (3 - 9g ginseng)**
- **Administer up to 2 hours before meal**
- **3 g dried root reduced postprandial hyperglycemia by 19-22%**

Vusdan V. Diabetes Care 2000:23;1221-1226. Vusdan V. Arch Int Med. 2000; 27:1009-1013.

Problems With Current Therapies

	Hypo-glycemia	Multiple doses	ADRs	Limits on population
MET		BID	GI	Y
Acarbose		TID	GI	
SFU	Y		Wt	
MEG	Y	TID	Wt	
TZD	Y		Wt, Edema	Y
INS	Y	QD-QID	Wt	

Problems With Current Therapies

- **Target only limited physiologic abnormalities**
- **Ineffective at preventing beta cell dysfunction**
- **Hypoglycemia**
- **All cause weight gain except metformin and alpha-glucosidase inhibitors**

New Insulins

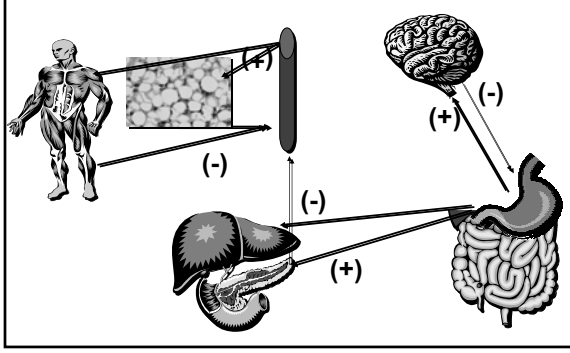
- **Insulin detemir (Levemir®)**
  - **Approval expected in 2005**
  - **Kinetics appear less variable than glargine and NPH**
  - **Not associated with weight gain in trials up to 12 months duration.**
- **Inhaled Insulin (Exubera®)**
  - **Awaiting completion of safety trials**
  - **Approval anticipated in 1 year**
  - **(+) weight gain; (-) pulmonary decline**

Incretin Mimetics

Exenatide

Liraglutide

Glucagon-like Peptide (GLP-1)



Exendin-4

Glucoregulatory actions

- **Glucose dependent enhancement of insulin secretion**
- **Glucose dependent inhibition of glucagon secretion**
- **Slows gastric emptying time (GET)**
- **Reduces caloric intake**
- **Promotes Beta-cell proliferation and creation of new islet cells**

Exenatide
by Eli Lilly

- **Synthetic Exendin-4**
- **Dose 0.8 mcg/kg subcutaneous injection twice daily**
- **Adverse effects**
  - **Nausea**

Exenatide Plus SFU and / or MET in Type 2 DM

- **Effect of addition of exenatide 0.8 μg/kg to**
  - **Metformin alone**
  - **Sulfonylurea alone**
  - **Both**
- **Regimen**
  - **Breakfast and Supper**
  - **Breakfast and Bedtime**
  - **Three times daily**
- **Duration 28 days**

Fineman MS et al. Diabetes Care. 2003;26:2370-7.

Exenatide Plus SUF and / or Metformin in Type 2 DM

	BID	AM HS	TID	Placebo
Fructosamine (μm aol/L)	- 45	- 39	- 46	- 5
A1c (%)	- 1.1	- .7	- 1.0	- .3
Mean Glucose(mg/dL)	- 79	- 58	- 61	- 11

Fineman MS et al. Diabetes Care. 2003;26:2370-7.

Liraglutide
by NovoNordisk

- **Subcutaneous once daily dose of 0.6 mg**
- **8 week trial in 35 persons with T2DM**
  - **Persons on oral SFU or diet therapy**

	FBG (mg/dL)	A1C change (%)	Wt change (kg, lbs)
Placebo	5.4	0.47	-0.9 (-1.98)
Liraglutide	-34.2	-0.33	0.07(.15)

Harder H. Diabetes Care 2004;27: 1915-1921.

DPP-IV Inhibitors

- **Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors**
  - **Inhibit the metabolism of GLP-1 to inactive form**
  - **Oral agents (LAF237 and MK-0431)**
  - **Dose dependent reduction in fasting glucose**
  - **A1C decreases up to 1.2 %**
  - **No N/V, hypoglycemia, or weight changes**

www.DiabetesInControl.com Accessed 3-5-05

Amylin Analogues

Pramlintide (Symlin)

Pramlintide (Symlin)

manufactured by Lilly

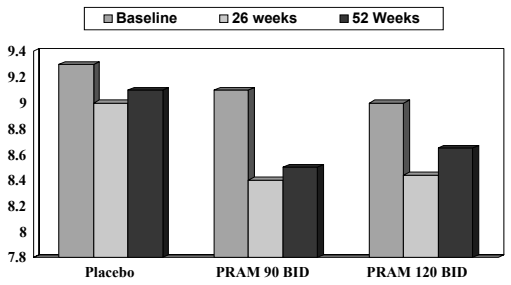
- Analogue of amylin
- Physiological effects same as amylin
  - –Suppress postprandial glucagon
  - –Slow GET
  - –Decrease energy intake
- 90 and 120 mcg BID subcutaneous injection
- 15 minutes prior to meals
- Primarily for postprandial control
  - –Peaks in 20 minutes; Duration of 3 hours

Pramlintide (Symlin)

- Adverse Effects
  - –Withdrawal due to ADRs (18%)
  - –Severe Hypoglycemia
  - – (9% vs 4% placebo T1DM)
  - – (2% vs 1% placebo T2DM)
  - –Nausea (47% vs 22% T1DM;
  - – 15-27% vs 17%)
  - –Headache (1%)
- Benefits
  - –Associated with -2.6 kg (-5.7 lb) weight change

Hollander P. Diabetes Care 2003: 26: 784-790.
http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b1_03_Medical%20Review%20Safety.htm

Pramlinitide (Symlin) – A1c Effect



Hollander P. Diabetes Care 2003: 26: 784-790..

Pramlinitide (Symlin)

- Role yet unclear
- Future trials should address
  - –Methods to reduce hypoglycemia
  - –Methods to reduce nausea
  - –Longer trials to assess sustained benefit and effect of removing drug

Summary

- Metformin: reduces CVD in diabetes
- Acarbose: reduces CVD in pre-diabetes
- Metformin helps stabilize weight
- Weight gain not associated with insulin detemir, exenatide, liraglutide, or pramlintide
- Cinnamon and ginseng reduce hyperglycemia

Rationale for Early Use of Combination Therapy

Bruce Trippe, MD

Summary: Combination Therapy

- Earlier intervention with combination therapy provides durable glycemic control and may reduce disease progression
- Clinical trials have supported the use of various combinations of TZDs, MET, and SU at submaximal doses

Cardiovascular (CV) Risk Factors Associated With Insulin Resistance

- Elevated blood pressure
- High triglyceride levels
- Low high-density lipoprotein (HDL) cholesterol
- Small, dense low-density lipoprotein (LDL) particles
- Elevated C-reactive protein (CRP)
- Microalbuminuria
- State of hypercoagulation
- Endothelial dysfunction

McFarlane SI et al. *J Clin Endocrinol Metab.* 2001;86:713-718.

Management of Insulin Resistance

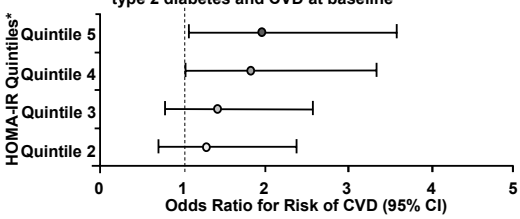
- Improve insulin sensitivity
  - –Caloric restriction; weight loss
  - –Exercise
  - –Medications
    - Thiazolidinediones
    - Metformin
    - Combination therapy

Management of CV Risk Factors

- Risk factor management
  - –Hypercholesterolemia (LDL) – statins, resins
  - –Low HDL, high triglycerides (TGs) – fibrates, niacin, statins
  - –Hypertension – ACEIs, ARBs, β-blockers
  - –Glycemic control
  - –Aggressively screen for and treat albuminuria and nephropathy
  - –Smoking cessation
  - –Aspirin

San Antonio Heart Study: Increased Insulin Resistance Associated With Increased CVD Risk

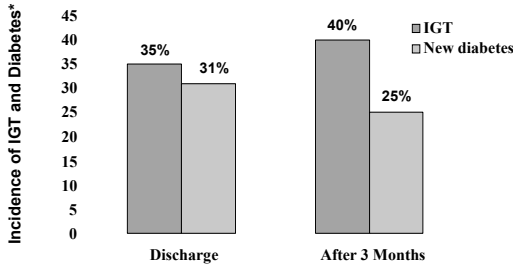
Association between HOMA-IR and 8-year risk of CV outcomes (CV death, MI, heart surgery, angina) in 2600 subjects free of type 2 diabetes and CVD at baseline



P(trend)=.0185
*Quintile of HOMA-IR adjusted for age, sex, ethnicity, LDL, triglyceride, HDL, SBP, smoking, alcohol consumption, leisure time exercise, and waist circumference (median split).
Adapted from Hanley AJG et al. *Diabetes Care.* 2002;25:1177-1184.

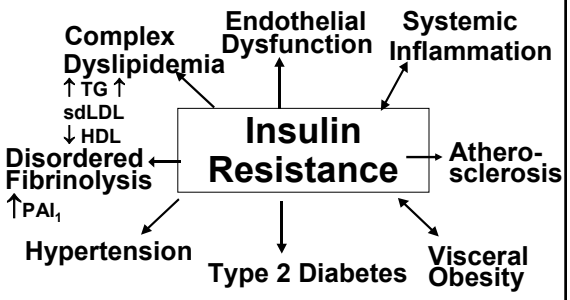
Discovery of IGT and Type 2 Diabetes After CAD or MI

Patients With Acute MI
Not Previously Known to Have Diabetes



*Oral glucose tolerance test. Norhammar A et al. *Lancet.* 2002;359:2140-2144.

The Metabolic Syndrome of Insulin Resistance



ADA. Consensus Development Conference on Insulin Resistance. *Diabetes Care.* 1998;21:310-314. Pradhan AD et al. *JAMA.* 2001;286:327-334.

Metabolic Syndrome: NCEP ATP III Criteria

Identifies a constellation of symptoms of which none alone has been shown to be a categorical risk factor

Risk Factor	*Defining Level*
✓Abdominal Obesity (waist circumference)	
Men	>40 inches
Women	>35 inches
✓Triglycerides	≥150 mg/dL

NCEP ATPIII. *JAMA.* 2001;285:2486-2497.

Metabolic Syndrome: NCEP ATP III Criteria

Identifies a constellation of symptoms of which none alone has been shown to be a categorical risk factor

Risk Factor	*Defining Level*
✓HDL Cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
✓Blood Pressure	≥130/≥85 mm Hg
✓Fasting Glucose	≥100 mg/dL

NCEP ATPIII. *JAMA.* 2001;285:2486-2497.

Metabolic Effects of Oral Antidiabetic Agents

	TZD	*MET*	*SU/MG*	*AGI*
Weight	↑ or ↔	↓ or ↔	↑	↔
LDL cholesterol	↑ or ↔	↓ or ↔	↔	↔
Small, dense LDL	↓	↔	↔	↔
HDL cholesterol	↑↑	↑ or ↔	↔	↔
Triglycerides	↓ or ↔	↓	↔	↔
Free fatty acids	↓↓↓	↓↓	↓	↔

TZD=thiazolidinedione; MET=metformin; SU=sulfonylurea; MG=meglitinide; AGI=alpha glucosidase inhibitor; ↑=increase; ↓=decrease; ↔=no effect. Lawrence JM et al. *Diabetes Care.* 2004;27:41-46. Luna B, Feinglos MN. *Am Fam Physician.* 2001;63:1747-1780. Parulkar AA et al. *Ann Intern Med.* 2001;134:61-71. Huber K et al. *Thromb Res.* 2001;103(suppl 1):S7-S19. Festa A et al. *Circulation.* 2000;102:42-47. O'Keefe JH et al. *Mayo Clin Proc.* 1999;74:171-180.

Metabolic Effects of Oral Antidiabetic Agents (continued)

	TZD	*MET*	*SU/MG*	*AGI*
Insulin resistance	↓↓	↓	↔	↔
PAI-1	↓↓	↓	↔	↔
C-reactive protein	↓↓	↓	↔	↔
Hypertension	↓ or ↔	↔	↔	↔
Microalbuminuria	↓	↔	↔	↔

TZD=thiazolidinedione; MET=metformin; SU=sulfonylurea; MG=meglitinide; AGI=alpha glucosidase inhibitor; PAI-1=plasminogen-activator inhibitor-1; ↑=increase; ↓=decrease; ↔=no effect. Haffner SM et al. *Circulation.* 2002;106:679-684. Luna B, Feinglos MN. *Am Fam Physician.* 2001;63:1747-1780. Parulkar AA et al. *Ann Intern Med.* 2001;134:61-71. Huber K et al. *Thromb Res.* 2001;103(suppl 1):S7-S19. Festa A et al. *Circulation.* 2000;102:42-47. O'Keefe JH et al. *Mayo Clin Proc.* 1999;74:171-180.